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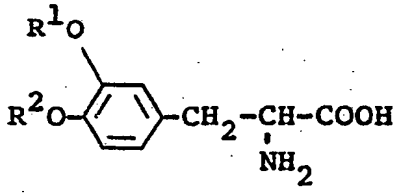
## (54) L-Dopa derivatives or their acid addition salts, process for producing same and their use.

(57) An L-dopa derivative represented by formula [I]



[I]

wherein one of $R^1$ and $R^2$ denotes a hydrogen atom and the other denotes a group of formula R-CO- in which R denotes an alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted aralkyl, lower alkoxy or optionally substituted aralkyloxy group.

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This invention relates to novel L-dopa derivatives, and more specifically, to novel L-dopa derivatives or their acid addition salts useful in the medical field, especially in the treatment of a series of diseases called Parkinson's disease or Parkinsonism, a process for producing same and their use.

L-Dopa has been developed as a precursor of dopamine to make up for deficiency in dopamine in the brain of patients with Parkinson's disease, and is now generally accepted as the first drug of choice in the field. Long-term therapy with L-dopa is, however, associated with a variety of problems, such as motor fluctuations, short duration of action, loss of drug responsiveness, etc. The diskinesia and end-of-dose deterioration ("wearing off") are probably the most common motor fluctuations seen in Parkinson's disease patients treated chronically with L-dopa. The dyskinesias mean abnormal involuntary movements such as chorea and athetosis observed in jaws, limbs, neck, etc, which often appear 1-2 hours after administration of L-dopa. These dyskinesias correlate with dose and blood concentration of L-dopa, so they are well managed by reducing the size of each individual dose or increasing frequency of dosing. The end-of-dose deterioration means repeating motor fluctuation with short period of relief and aggravation of the disease, which are parallel to the blood level of L-dopa. Smaller, more frequent doses of L-dopa usually improve patients experiencing end-of-dose deterioration. The other problems, such as short duration of action or another kind of the drug-induced motor fluctuations, are indicated to attribute to a rapid elimination of L-dopa from blood (refer to Eur. J. Clin. Pharmacol., vol. 25, p. 69, 1983 and Experientia, vol. 40, p. 1165, 1984). In order to solve the above problems, it is vital to suppress a rapid increase in blood level of L-dopa and attain a long-lasting blood level of L-dopa with less fluctuation (see Neurology, vol. 34, p. 1131, 1984 & vol. 36, p. 739, 1986 and N. Eng. J. Med., vol. 30, p. 484, 1984).

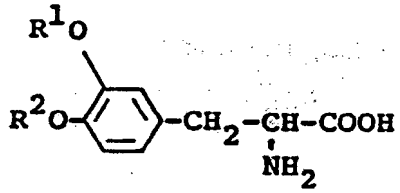
When L-dopa itself is administered to the patients, the blood level of L-dopa rapidly increases and falls; it is therefore difficult to cope with the foregoing problems. For this reason, L-dopa is often administered up to 7 times a day or intravenously injected continually. These treatments, however, are indeed a great burden on the patients.

A number of attempts have been hitherto made to produce various L-dopa derivatives, especially to make prodrugs of L-dopa on the premise that they are converted to L-dopa in vivo. However, there is no clinically used L-dopa prodrug which has been successfully designed to accomplish a long-lasting blood level and durable efficacy of L-dopa [see J. Med. Chem., vol. 20, p. 1435, 1977, ibid., vol. 29, p. 687, 1986, Eur. J. Med. Chem., vol. 20, p. 459, 1985, Japanese Laid-open Patent Applications No. 9567/1972 (British Patent No. 1347375), No. 31949/1972 & No. 72150/1973 (British Patent No. 1378419) and U.S. Patent No. 3939253].

It is an object of this invention to solve the problems in L-dopa therapy by suppressing adverse effects caused by the rapid and excessive increase in blood level of L-dopa when administering L-dopa, maintaining a clinically effective blood level of L-dopa for a long period of time and attaining a favorable pharmacokinetic profile of L-dopa with less fluctuation.

In order to solve the foregoing problems, the present inventors have made extensive studies to prepare prodrugs of L-dopa, and consequently discovered that a monoester of L-dopa catechol represented by formula [I] below does not cause a rapid and excessive increase in blood level of L-dopa on oral administration, maintains a clinically effective blood level of L-dopa for a long period of time and gives a favorable pharmacokinetic profile of L-dopa with less fluctuation. Said discovery has led to completion of this invention.

Namely, this invention is to provide a novel L-dopa derivative represented by formula [I]



[I]

wherein one of $R^1$ and $R^2$ denotes a hydrogen atom and the other denotes a group of formula R-CO- in which R denotes an alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted aralkyl, lower alkoxy or optionally substituted aralkyloxy group,
and its acid addition salt, a process for producing same and its use in the treatment of Parkinson's disease.

Various terms used in the specification and appended claims and suitable examples thereof are explained hereinafter.



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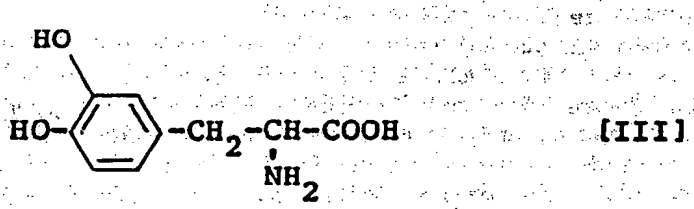
The compound of formula [I] can be present in the form of an acid addition salt based on the amino group present. Examples of such acid addition salt are salts of inorganic acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, perchloric acid and phosphoric acid; and salts of organic acids such as p-toluenesulfonic acid, benzenesulfonic acid, methanesulfonic acid and trifluoroacetic acid. Pharmaceutically acceptable acid addition salts are especially preferable.

The compound of formula [I] and its salt provided by this invention can be produced by reacting L-dopa that may be protected with an acylating agent represented by formula [II]

R-CO-Q [II]

wherein Q denotes a leaving group and R is as defined above,
then removing the protecting group present, and if required, converting the resulting L-dopa derivative of formula [I] into its acid addition salt.

The "L-dopa that may be protected" here referred to means L-dopa represented by formula [III]



[III]

wherein a carboxyl group, an amino group and/or one of the two hydroxyl groups (i.e. the hydroxyl group of which acylation is not desired) present on the catechol moiety, being reactive functional groups of L-dopa, may be protected by a protecting group known per se in the field of a peptide chemistry. Thus, Examples of the protecting group of the amino group are benzyl, benzyloxycarbonyl, tert-butoxycarbonyl and p-nitrobenzyloxycarbonyl groups. Examples of the protecting group of the carboxyl group are benzyl, benzhydryl, p-nitrobenzyl, tert-butyl and allyl groups. Examples of the protecting group of the hydroxyl group are benzyl, methoxymethyl, benzyloxycarbonyl, tert-butyldimethylsilyl groups.

The above protecting groups can be introduced in L-dopa of formula [III] by a usual method in the field of the peptide chemistry.

However, the reaction between L-dopa of formula [III] and the acylating agent of formula [II] fully proceeds by selecting the amount of the acylating agent and the other reaction conditions without protecting the reactive functional groups of L-dopa. Accordingly, from the economical aspect of the procedure, it is convenient to use L-dopa in unprotected form.

On the other hand, the leaving group (Q) in the acylating agent of formula [III] can be an acid residue of a carboxylic acid ester-forming reactive derivative such as a halide or an acid anhydride. Examples thereof are halogen atoms such as chlorine, bromine and iodine; and acyloxy groups such as ethoxycarbonyloxy, acetoxy, propionyloxy, isopropionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, cyclopropanecarbonoyloxy and 2-methylcyclo propancarbonoyloxy groups.

The reaction between L-dopa which may be protected and the acylating agent of formula [II] can be performed, for example, at a reaction temperature of about -20 °C to about 100 °C, preferably about -10 °C to about 70 °C in such a solvent as not to adversely affect the reaction, for example, dioxane, tetrahydrofuran, ethyl acetate, acetonitrile, dimethylformamide, benzene, toluene, ethyl ether, chloroform, methylene chloride, trifluoroacetic acid, or a mixture thereof. Though the reaction is influenced by the type of the acylating agent, the reaction temperature and the type of the solvent, it is usually finished in 30 minutes to 48 hours.

The amount of the acylating agent of formula [II] varies depending on whether or not L-dopa as a starting material is protected, or the type of the acylating agent and the reaction conditions. Generally, it can be 0.8 to 10 mols per mol of L-dopa which may be protected.

Particularly, when L-dopa with two hydroxyl groups of the catechol moiety unprotected (the carboxyl group and/or amino group of L-dopa may be protected) is used as a starting material, it is advisable that the amount of the acylating agent of formula [II] is about 0.9 to about 1.1. mols per mol of said L-dopa in order to suppress diacylation of the catechol moiety, and it is preferable to use said acylating agent in a substantially equimolar amount.

When L-dopa with the amino group unprotected (the carboxyl group and/or one hydroxyl group may be protected), above all, the unprotected L-dopa, is used as a starting material, it is convenient to conduct the



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or without sugar coating, suppository or capsule, or a common liquid administration form such as a solution, suspension or emulsion. Pharmaceutical compositions can be subjected to ordinary pharmaceutical treatment, e.g. sterilization and/or contain antiseptics, stabilizers, wetting agents, emulsifying agents, salts to adjust an osmotic pressure and buffering agents.

The preparation is produced to contain 1 to 99% by weight, preferably about 25 to about 95% by weight of the active ingredient of formula [I] and 1 to 99% by weight, preferably about 5 to about 75% by weight of the inactive carrier or diluent.

The preparation can further contain other substances useful for medical treatment. Examples thereof are L-aromatic amino acid decarboxylase inhibitors having an activity to suppress peripheral decarboxylation of L-dopa, such as (-)-L-alpha-hydrazino-3,4-dihydroxy-alpha-methylhydrocinnamic acid (generic name: carbidopa) and DL-serine-2-{2,3,4-trihydroxyphenyl)methyl}hydrazide (generic name: benserazide). These L-aromatic amino acid decarboxylase inhibitors can be contained in a proportion of generally 1 to 1/15 mol, preferably 1/2 to 1/10 mol per mol of the L-dopa derivative of formula [I] or its acid.

When the L-dopa mono-O-acyl product in this invention is used as a treating agent of Parkinson's disease, the dose and the flucuency of administration vary with the degree of symptoms, the age and weight of patients and if used with other medicines, the type of medicines. Usually, in the oral administration, it is advisable that the medicine is administered to an adult patient at a dose of 0.5 to 50 mg/kg a day at a time or in several divided portions.

Test Examples of the compound in this invention are described hereinafter to concretely make clear its availability.

The drawings quoted in Test Examples below are explained hereinafter.

Figure 1 illustrates change with time of a blood level of L-dopa in orally administering L-dopa to rats.

Figure 2 illustrates change with time of a blood level of L-dopa in orally administering Compound A to rats.

Figure 3 illustrates change with time of a blood level of L-dopa in orally administering Compound B to rats.

Fugure 4 illustrates change with time of a blood level of L-dopa in orally administering L-dopa to Beagle dogs.

Figure 5 illustrates change with time of a blood level of L-dopa in orally administering Compound A to Beagle dogs.

Figure 6 illustrates change with time of a blood level of L-dopa in orally administering Compound B to Beagle dogs.

Figure 7 illustrates change with time of a blood level of L-dopa in intravenously administering Compound A ( O ) and L-dopa (●) to rats.

Figure 8 illustrates change with time of amounts of Compound A ( O ) and L-dopa (●) after injection of Compound A, and amount of L-dopa (●) after injection of L-dopa in the lumen of the small intestine of rats according to an in situ ligating loop method.

Figure 9 illustrates change with time of amounts of Compound A (Δ) and L-dopa ( O ) after injection of Compound A, and amount of L-dopa (●) after injection of L-dopa in the tissue of the small intestine of rats according to an in situ ligating loop method.

Drugs used in Test Examples below have the following meanings.

Compound A: 4-O-pivaloyl-L-dopa

Compound B: 4-O-(1-methylcyclopropanecarbonyl)-L-dopa

## Test Example 1

### Measuring blood levels of L-dopa after oral administration of drugs (rats)

Seven to eight week-old SD-strain male rats (n = 4) were previously fasted for 18 hours. A preparation (a preparation obtained by dissolving or suspending 20 mg of L-dopa as a control drug or the equimolar amount of each of the test drugs together with 4 mg of carbidopa in 20 ml of water containing 0.5% sodium carboxymethylcellulose and 0.1% Tween 80) was orally administered to the rats at a dose of 10 mg/kg (10 mg eq./kg, calculated as L-dopa). Immediately after administration, or 15, 30, 60, 90, 120, 150, 180, 240,



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Test Example 4

Measuring concentrations of L-dopa in the lumen and tissue of the small intestine by an in situ ligating loop method (rats)

Eight week-old male rats (n = 3) were fasted overnight before the test, and then under ether anesthesia, were incised at the abdomen. An acute loop of 8 cm length was ligated in the jejunum. Compound A (1.47 mg) or 1.00 mg of L-dopa as a control drug was suspended in 0.5 ml of 0.5% sodium carboxymethylcellulose together with 0.4 mg of carbidopa, and the suspension was injected into the loop. The loop was returned in the abdominal cabity and the cut portion was then sewn. After a fixed time, the loop was taken out again and the content in the loop was well washed with a ice-cooled physiological saline. The intestinal tissue was homogenated with ethanol containing hydrochloric acid in a 19-fold amount per tissue. The washing liquid and supernatant of the homogenate (3000 rpm, 10 minutes, 4 °C) were properly diluted. In the resulting solutions, the concentration of L-dopa was determined as in Test Example 1 and the concentration of Compound A as follows, respectively. To the solution was added 0.5 volume of an o-phthalaldehyde reagent [prepared by dissolving 8 mg of o-phthalaldehyde and 8 mg of N-acetylcysteine in a mixture of 200 µl of methanol and 800 µl of a 81 mM boric acid buffer solution (pH 8.0)] to give a fluorescent derivative of Compound A. The concentration of Compound A in the samples was measured by HPLC with a fluorescence detector [column: Zorbax $C_8$ (5µm), 250 mm x 4.6 mm ø, mobile phase: methanol-containing McIlvaine buffer solution, flow rate: 1.0 ml/min., detecting wavelength: exc. 340 nm/emi. 450 nm].

The results are shown in Figures 9 and 10. The amount of L-dopa in the lumen (washing liquid) and tissue (homogenate) of the small intestine after administration of Compound A was retained for a longer time with less fluctuation than that after administration of L-dopa. Moreover, as the concentration was kept low, it can be expected to decrease gastro-intestinal side effects of a digestive system such as nausea, vomiting, anorexia and ulcer which are problems in clinical application of L-dopa.

Test Example 5

Acute toxicity

(1) Oral administration

Each of the test drugs was suspended in a 0.5% sodium carboxymethylcellulose solution containing 0.1% Tween 80 and orally administered to each of ddY-strain male mice (body weight 24 to 31 g, n = 5), and a mortality up to 1 week after administration was observed. Toxicity of test compounds (Compounds A and B) was extremely low. The $LD_{50}$ value was 6 g/kg or more in both cases. Where L-dopa as a control drug was orally administered, its $LD_{50}$ value was 3.2 g/kg.

(2) Intraperitoneal administration

Each of the test drugs was suspended in a sterilized physiological saline and intraperitoneally administered to ddY-strain male mice (body weight 24 to 29 g, n = 5), and a mortality up to 1 week after administration was observed.

Toxicity of the test compound (Compound A) was very low, and no case of death was observed in the intraperitoneal administration at a dose of 1800 mg/kg either. Where L-dopa as a control drug was intraperitoneally administered at a dose of 1250 mg/kg, the two of five mice were dead. In the intraperitoneal administration of L-dopa at a dose of 1800 mg/kg, all the test mice were dead.

The following examples illustrate this invention more specifically.



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IR $\nu_{max}^{KBr}$ ($cm^{-1}$): 3088, 2968, 1761, 1665, 1575, 1446, 1413, 1356, 1305, 1248, 1149
MS (FAB) m/z: 282 [$M^+$ + 1]
NMR ($CD_3OD$) $\delta$ : 0.96(3H, t, J=7.4Hz), 1.45+1.46 (2H, sexX2, J=7.4Hz), 1.70+1.71(2H, qX2, J=7.4Hz), 2.59+2.60(2H, tX2, J=7.4Hz), 3.01+3.02(1H, ddX2, J=14.5Hz & 8.3Hz), 3.24+3.28(1H, ddX2, J=14.5Hz & 4.9Hz), 4.11+4.12 (1H, ddX2, J=8.3Hz & 4.9Hz), 6.75+7.02(1H, ddX2, $J^1$=8.0Hz & 1.9Hz, $J^2$=8.2Hz & 2.0Hz), 6.86+6.91 (1H, dX2, J=1.9Hz & 2.0Hz), 6.93+ 6.90(1H, dX2, J=8.0Hz & 8.2Hz)

Example 5

Using 1.00 g of L-dopa, 0.5 ml of a 70% perchloric acid aqueous solution and 3.00 g of 3,3-dimethylbutyryl chloride as starting materials and 30 ml of dioxane as a solvent, the reaction was performed at room temperature for 17 hours. The same treatment as in Example 1 was then conducted to afford 0.23 g (yield 15.6%) of 4-O-(3,3-dimethylbutyryl)-L-dopa (Compound E).
m.p.: 255-258° C (decomp.)
IR $\nu_{max}^{KBr}$ ($cm^{-1}$): 3100, 2962, 1752, 1611, 1521, 1443, 1332, 1296, 1244, 1116, 831
MS (FAB) m/z: 296 [$M^+$ + 1]
NMR ($CD_3OD$) $\delta$ : 1.13+1.14(9H, sX2), 2.47+2.48(2H, sX2), 3.03+3.06(1H, ddX2, J=14.3Hz & 8.9Hz), 3.28+3.31(1H, ddX2, J=14.3Hz & 4.4Hz), 4.20+4.22(1H, ddX2, J=8.9Hz & 4.4Hz), 6.88-6.96(2H, m), 6.77+7.03(1H, ddX2, $J^1$=8.2Hz & 2.2Hz, $J^2$=8.0Hz & 1.9Hz)

Example 6:

using 1.00 g of L-dopa, 0.5 ml of a 70% perchloric acid aqueous solution and 5.00 g of octanoyl chloride as starting materials and 30 ml of ethyl acetate as a solvent, the reaction was performed at room temperature for 18 hours. Thereafter, the same treatment as in Example 1 was conducted to obtain 0.50 g (yield 30.9 %) of 4-O-octanoyl-L-dopa (Compound F).
m.p.: 231-233° C (decomp.)
IR $\nu_{max}^{KBr}$ ($cm^{-1}$): 3124, 2932, 2860, 1761, 1665, 1575, 1413
MS (FAB) m/z: 324 [$M^+$ +1]
NMR ($CD_3OD$) $\delta$ : 0.95(3H, t, J=7.4Hz), 1.25-1.50 (8H, m), 1.70(2H, q, J=7.4Hz), 2.54+2.56(2H, tX2, J=7.4Hz), 3.12 (1H, dd, J-14.4Hz & 4.4Hz), 4.23+4.26(1H, ddX2, J=9.0Hz & 4.4Hz), 6.86-6.99(2H, m), 6.80+7.03(1H, ddX2, $J^1$=8.3Hz & 1.9Hz, $J^2$=7.9Hz & 2.1Hz)

Example 7:

One gram of L-dopa was suspended in 20 ml of ethyl acetate and 0.5 ml of a 70% perchloric acid aqueous solution was added under stirring with ice cooling at 5 to 10° C to form a homogeneous solution. To the solution was added dropwise 5.00 g of palmitoyl chloride over a period of 5 minutes. After the addition, the reaction was run at room temperature for 17 hours. To the reaction mixture was added 50 ml of petroleum ether, and the supernatant liquid was removed by decantation. Subsequently, the oily precipitate was washed again with 20 ml of petroleum ether. The precipitate was added to 50 ml of water, and a 1N sodium hydroxide aqueous solution was added under stirring with ice cooling to adjust pH to 5.0 to 5.5. The product was collected by filtration to give a 1.20 g (yield 54.3%) of 4-O-palmitoyl-L-dopa (Compound G).
m.p.: 218-220° C (decomp.)
IR $\nu_{max}^{KBr}$ ($cm^{-1}$): 3082, 2926, 1761, 1668, 1578, 1446, 1413, 1356, 1146, 1119
MS (FAB) m/z: 436 [$M^+$ + 1]
NMR ($CD_3OD$) $\delta$ : 0.87(3H, t, J=6.4Hz), 1.20-1.40 (24H, m), 1.71(2H, q, J=6.7Hz), 2.58+2.59(2H, tX2, J=6.7Hz), 3.02-3.13(1H, m), 3.20-3.22(1H, m), 4.10-4.3(1H, m), 6.77+7.30(1H, ddX2, J=8.0Hz & 2.0Hz), 6.90-6.96(2H, m)

Example 8:

The reaction was performed as in Example 7 except using 6.00 g of dodecanoyl chloride instead of



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minutes while keeping pH at 6.0 to 8.0. After the addition was over, the mixture was stirred at room temperature for 1 hour and diluted with 50 ml of ethyl acetate. Subsequently 2N hydrochloric acid was added to adjust pH to 2.0. An organic layer was taken out, water-washed and dried over anhydrous magnesium sulfate. After the drying agent was separated by filtration, the solvent was evaporated under reduced pressure. When the residue was purified by silica gel column chromatography (Wakogel C-100, 120 g, eluted with methylene chloride/methanol = 5/1), 2.60 g (yield 62.6%) of N-benzyloxycarbonyl-mono-O-pivaloyl-L-dopa was obtained as a pale yellow glass solid.

IR $\nu_{max}^{KBr}$ ($cm^{-1}$): 3376, 2980, 1734, 1614, 1344, 1293, 1236, 1059, 738, 699

NMR ($CDCl_3$) $\delta$ : 1.35 + 132(9H, sX2), 2.92-3.12(2H, m), 4.41-4.65(1H, m), 5.01-5.19(2H, m), 5.41(1H, d, J = 7.4Hz), 6.59-7.41(8H, m)

One gram of the above obtained mono-O-pivaloyl product was dissolved in 50 ml of methanol, and the solution was catalytically reduced at a hydrogen pressure of 5 $kg/m^2$ in the presence of 0.1 g of a 5% palladium/carbon catalyst. After the catalyst was separated by filtration, the solvent was evaporated under reduced pressure. There resulted 0.41 g (reduction yield 60.5%) of 4-O-pivaloyl-L-dopa. The spectral data of said compound completely agreed with that of the compound obtained in Example 1.

Example 14:

(a) N-benzyloxycarbonyl-L-dopa benzyl ester (852 mg) was dissolved in 20 ml of acetone, and 52 mg of sodium iodide, 254 mg of benzyl chloride and 622 mg of potassium carbonate were added. Subsequently, the mixture was refluxed in at atmosphere of argon for 17 hours with stirring. After the reaction was over, the inorganic salt was removed by filtration. The filtrate was concentrated under reduced pressure, and the residue was purified by liquid chromatography [Lobar column Si 60 (tradename for a product manufactured by Merck), elution solvent: hexane/ethyl acetate = 10/1 to 6/11. There resulted the following two isomers. [The structures of both the isomers were confirmed by O-methylating each of the isomers with methyl iodide and potassium carbonate in acetone, followed by catalytic reduction in methanol in the presence of a 10% palladium/carbon catalyst to form corresponding 4-O-methyl-L-dopa or 3-O-methyl-L-dopa, and comparing each of the compounds with an authentic sample synthesized separately. (J. Org. Chem., vol. 21, pp. 4696-4698, 1961)]

Two isomers:

N-benzyloxycarbonyl-3-(3-benzyloxy-4-hydroxy)phenyl-L-alanine benzyl ester

Amount: 354 mg (pale yellow oily product, yield 42%)

IR $\nu_{max}^{neat}$ ($cm^{-1}$): 3376, 2926, 1722, 1518, 1458, 1389, 1344, 1275, 1236, 1197, 1122, 1059, 1026, 741, 699

MS (FAB) m/z: 512 [$M^+$ + 1], 378 (base peak)

NMR ($CDCl_3$) $\delta$ : 3.04(2H, d, J = 6.1Hz), 4.65-4.68(1H, m), 4.89-5.15(6H, m), 5.22(1H, d, J = 8.1Hz), 5.56(1H, s), 6.52(1H, dd, J = 8.1Hz & 1.7Hz), 6.63(1H, d, J = 1.7Hz), 6.77(1H, d, J = 8.1Hz), 7.32-7.40(15H, m)

N-benzyloxycarbonyl-3-(4-benzyloxy-3-hydroxy)phenyl-L-alanine benzyl ester

Amount: 310 mg (pale yellow oily product; yield 36%)

IR $\delta_{max}^{neat}$ ($cm^{-1}$): 3412, 3070, 3040, 2744, 1728, 1593, 1515, 1458, 1389, 1341, 1275, 1128, 1059, 1026, 915, 855, 738, 699

MS (FAB) m/z: 512 [$M^+$ + 1], 167 (base peak)

NMR ($CDCl_3$) $\delta$ : 3.01(2H, d, J = 5.6Hz), 4.65(1H, m), 5.04(2H, s), 5.07(2H, s), 5.14(2H, s), 5.22(1H, d, J = 8.2Hz), 5.59(1H, s), 6.46(1H, dd, J = 1.9Hz & 8.1Hz), 6.66(1H, d, J = 1.9Hz), 6.73(1H, d, J = 8.1Hz), 7.25-7.40(15H, m)

(b) The 3-benzyloxy produce (208 mg) obtained in Example 14-(a) was dissolved in dimethylformamide, and 126 mg of 4-dimethylaminopyridine, 124 mg of triethylamine and 148 mg of pivaloyl chloride were added. The mixture was stirred with heating at 100 °C for 35 minutes. After the reaction was over, ethyl acetate and water were added to the reaction liquid, and the organic layer was washed with a saturated sodium chloride solution. The resulting solution was dried over anhydrous magnesium sulfate, followed by evaporating the solvent. The residue was taken out, purified by thin layer chromatography [Kiesel gel $60F_{254}$ Art 5744 (Merck), developing solvent: hexane/ethyl acetate = 10/3], and recrystallized from a mixture of ethyl ether, isopropyl ether and hexane.

There resulted 110 mg (yield 45%) of N-benzyloxy-3-(3-benzyloxy-4-pivaloyloxy)phenyl-L-alanine benzyl ester.

m.p.: 71-72 °C

IR $\nu_{max}^{KBr}$ ($cm^{-1}$): 1755, 1716, 1509, 1461, 1395, 1350, 1287, 1266, 1215, 1188, 1158, 1122, 1056,



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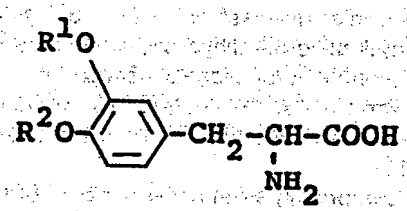
That is, the drugs of this invention, after administration, keep a clinically effective blood level of L-dopa for a long period of time without abrupt increase or rapid elimination of blood level of L-dopa. Further, bioavailability of the drugs in this invention is good, and it is also possible to decrease the dose as a prodrug, calculated as L-dopa being its parent compound. Still further, as the drugs of this invention have very low toxicity, they are extremely useful for the medical treatment of the Parkinson's disease against which patients have to take medicines for a long period of time.

## Claims

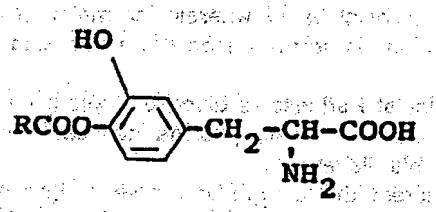
1. An L-dopa derivative represented by formula [I]



[I]

wherein one of $R^1$ and $R^2$ denotes a hydrogen atom and the other denotes a group of formula R-CO- in which R denotes an alkyl, alkenyl, optionally substituted cycloalkyl, optionally substituted phenyl, optionally substituted aralkyl, lower alkoxy or optionally substituted aralkyloxy group, and its acid addition salt.

2. The L-dopa derivative and its acid addition salt of claim 1 which is represented by formula [I-a]



[I-a]

wherein R is as defined in claim 1.

3. The L-dopa derivative and its acid addition salt of claim 1 wherein R is a linear or branched $C_1$-$C_{19}$ alkyl, $C_2$-$C_{19}$ alkenyl, $C_3$-$C_7$ cycloalkyl, phenyl, $C_7$-$C_{12}$ aralkyl, $C_1$-$C_6$ alkoxy or $C_7$-$C_{12}$ aralkyloxy group, provided the cycloalkyl, phenyl, aralkyl or aralkyloxy group may have one or two substituents selected from the group consisting of $C_1$-$C_4$ alkyl and $C_1$-$C_4$ alkoxy groups and a halogen atom.

4. The L-dopa derivative and its acid addition salt of claim 3 wherein R is a branched $C_3$-$C_5$ alkyl or linear $C_4$-$C_{15}$ alkyl group, or a $C_3$-$C_6$ cycloalkyl group which may be substituted with one or two $C_1$-$C_4$ alkyl groups.

5. The L-dopa derivative and its acid addition salt of claim 3 wherein R is a branched $C_3$-$C_5$ alkyl group or a $C_3$-$C_6$ cycloalkyl group which may be substituted by one $C_1$-$C_4$ alkyl group.

6. The L-dopa derivative and its acid addtion salt of claim 5 wherein R is a tert-butyl, cyclopropyl or 1-methylcyclopropyl group.

7. The L-dopa derivative and its acid addition salt of claim 6 wherein R is a tert-butyl group.

8. The L-dopa derivative and its acid addition salt of claim 1 which are 3-(3-hydroxy-4-pivaloyloxy)-phenyl-L-alanine, 3-(3-hydroxy-4-cyclopropanecarbonyloxy)-phenyl-L-alanine, 2-{3-hydroxy-4-(1-methyl-cyclopropanecarbonyl)oxy}phenyl-L-alanine and their acid addition salts.

9. A process for producing the L-dopa derivative represented by formula [I] recited in claim 1 or its acid addition salt, which comprises reacting L-dopa which may be protected with an acylating agent represented by formula [II]

R-CO-Q [II]



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then removing the protecting group present, and if required, converting the resulting L-dopa derivative of formula [I] into its acid addition salt.

2. The process of claim 1 wherein L-dopa is reacted with the acylating agent of formula [II] in the presence of at least 1 mol of a base per mol of said L-dopa.



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Fig. 3

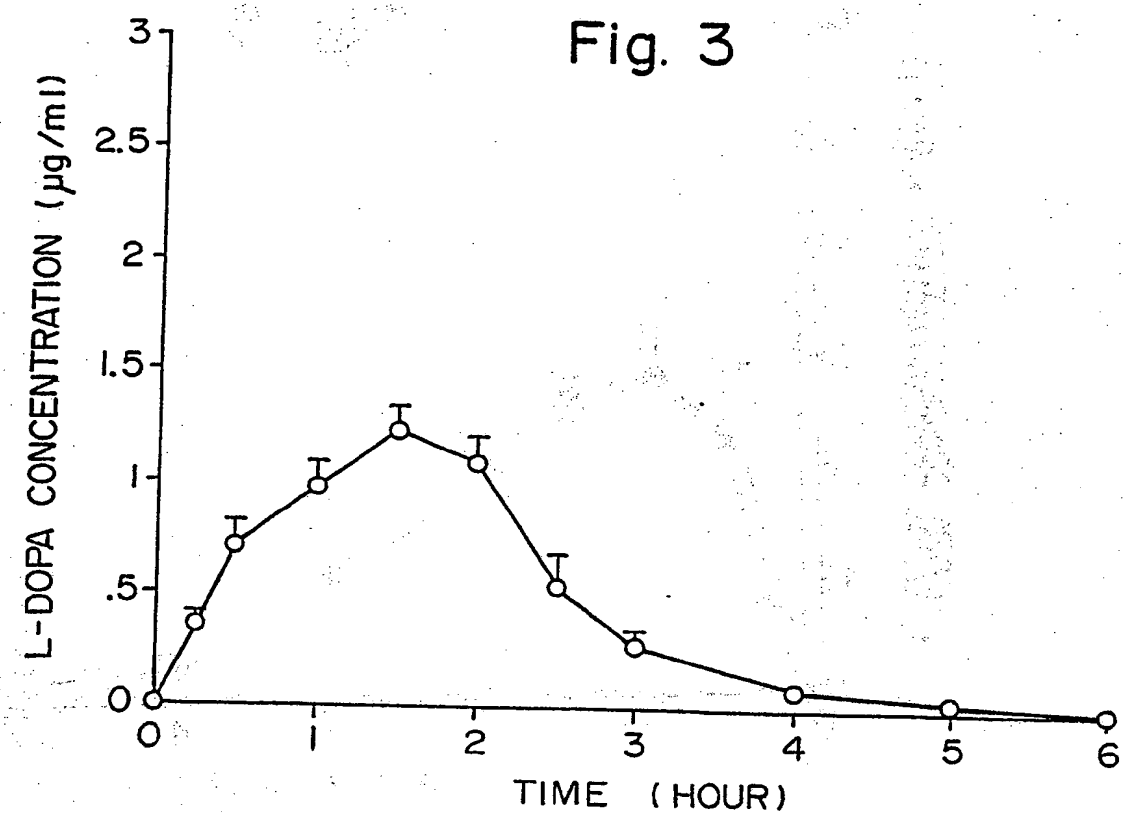


Fig. 4

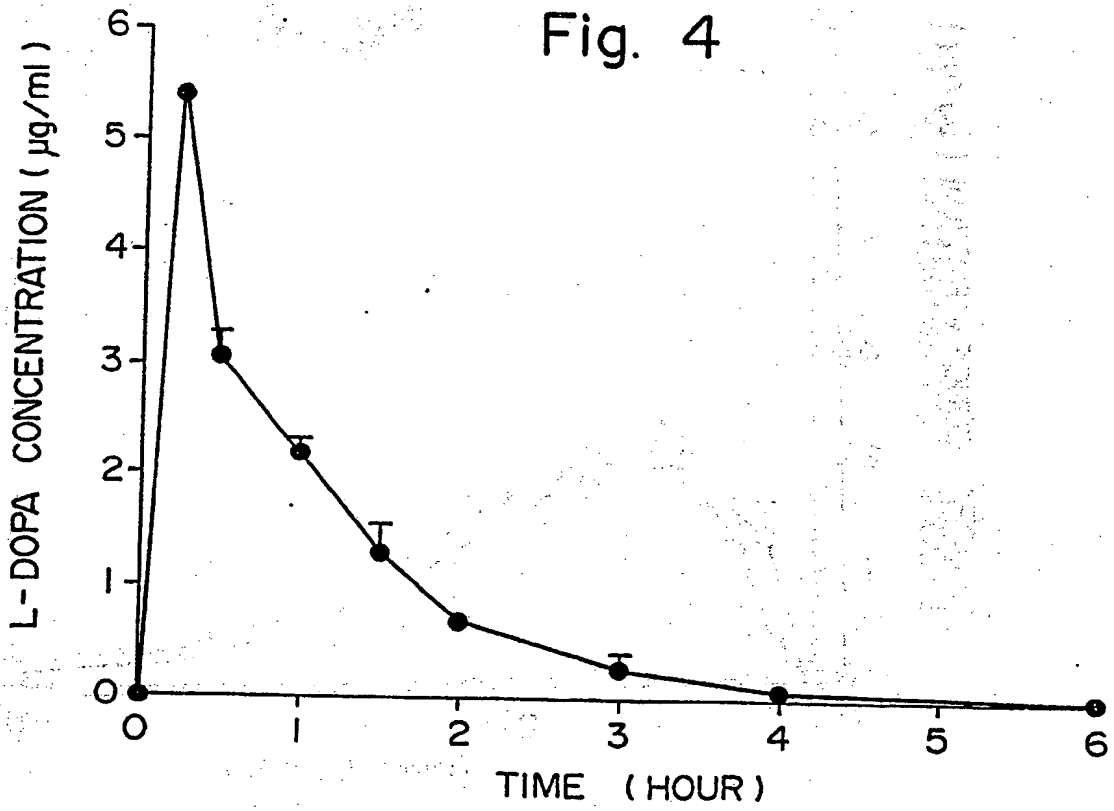


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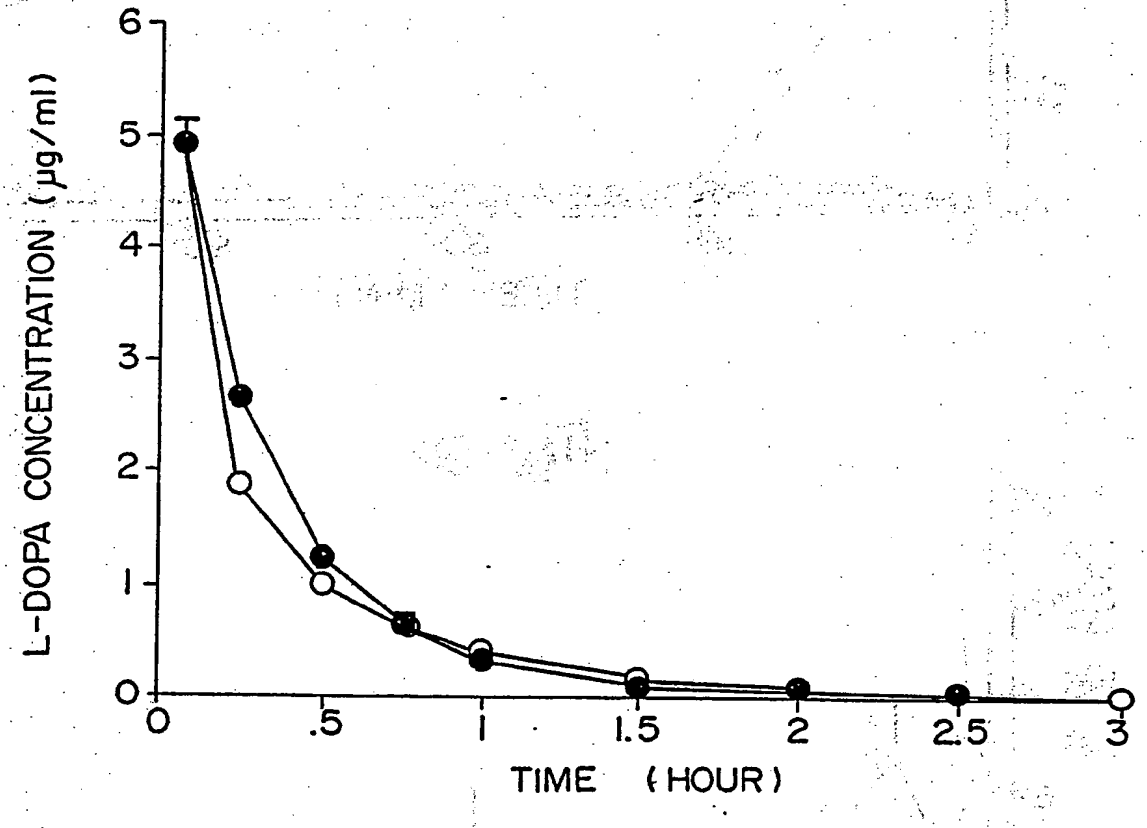
Fig. 7

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European Patent Office

# PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number: EP 88 11 5183

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.4) |
|---|---|---|---|
| A,D | GB-A-1 378 419 (LANNACHER HEIL-MITTEL GmbH)<br>* Whole document *<br>-- | 1,9, 11-19 | C 07 C 101/77<br>A 61 K 31/215 |
| A,D | US-A-3 939 253 (N.S. BODOR et al.)<br>* Whole document *<br>-- | 1,9, 11-19 | |
| A | US-A-2 868 818 (K. PFISTER et al.)<br>* Claim 1 *<br>-- | 1 | |
| A | J. ORG. CHEM., vol. 40, no. 23, 1975, page 3465<br>D.S. KEMP et al.: "Peptide Bond formation by the prior amine capture principle"<br>* Whole document *<br>-- | 1 | |
| | ./. | | |

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 C 101/00
A 61 K 31/00

## INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-19

Claims searched incompletely:

Claims not searched: 20-22

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| The Hague | 09-12-1988 | HELPS |

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